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Formulation of medicines for children

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The development of age-adapted dosage forms and taste-masking of bitter-tasting drugs administered orally for children, are formidable challenges for formulation scientists. Childhood is a period of maturation requiring knowledge of developmental pharmacology to establish dose but the ability of the child to manage different dosage forms and devices also changes. Paediatric formulations must allow accurate administration of the dose to children of widely varying age and weight. Whilst the oral route will be preferred for long term use and the intravenous route for the acutely ill, many of the dosage forms designed for adults, such as oro-dispersible tablets, buccal gels and transdermal patches, would also benefit children if they contained an appropriate paediatric dose. The age at which children can swallow conventional tablets is of great importance for their safety. Liquid medicines are usually recommended for infants and younger dhildren so the ability to mask unpleasant taste with sweeteners and flavours is crucial. More sophisticated formulations such as granules and oro-dispersible tablets may be required but there will be limitations on choice and concentration of excipients. There are many gaps in our knowledge about paediatric formulations and many challenges for the industry if suitable preparations are to be available for all ranges. A CHMP points to consider document is soon to be released. More research and clinical feedback are important because a formulation with poor acceptability may affect compliance, prescribing practice and ultimately commercial viability.

Introduction

In pharmacology and clinical paediatrics the focus is on the active drug substance (or active pharmaceutical ingredient (API)) when determining dosage, clinical effects and adverse drug reactions. However, the formulation is fundamentally important since it determines, in practice, whether the dose can be successfully delivered to the paediatric patient. Moreover, it is important to consider the formulation excipients and the potential for any adverse effects in this potentially vulnerable age group.

The development of formulations which are appropriate for children can present significant challenges to the pharmaceutical scientist. Unlike in adults, where oral solid dosage forms such as tablets or capsules will be acceptable to the majority of patients, potential paediatric patients may include neonates, newborn, toddlers, young children and adolescents, and as such, will have widely varying needs. The development of multiple dosage forms for different ages will rarely be commercially viable and liquid formulations, which can be given to a broad age group, present particular pharmaceutical challenges. For example, taste masking a bitter-tasting drug is a major formulation hurdle which can be very costly and may not be totally achievable.

Some considerations for the development of acceptable paediatric drug formulations are discussed below.

Requirement for dosage forms

There are various reasons for the formulation of drugs into appropriate dosage forms; one of the most important relates to accurate measurement of the dose. Many active drugs are very potent and only require milligram or microgram amounts to be administered. For children

the amount of drug required for the dose varies with age and weight. Active drugs must be diluted in a vehicle which allows accurate and convenient dose measurement. Active drugs must also be protected during their shelf life from degradation, for example by oxygen and humidity and, when administered orally, may require protection from degradation by gastric acid. It may be necessary to conceal taste and smell and to produce liquid preparations of insoluble or unstable drugs. There may be a requirement for rate controlled action or optimization of delivery of topical or inhalational drugs and those delivered by injection must be sterilized.

Ages and abilities

Childhood is characterized by periods of rapid growth, maturation and development. The ability to handle active drugs changes during childhood and is recognized in developmental pharmacology. There is a change in the magnitude of dose required during childhood and adolescence which may be fifty-fold. There are also significant changes in the ability to handle different dosage forms with small volume liquid medicines being appropriate for oral use in the younger age groups; liquid medicines and fast dissolving 'melt' formulations suitable for most ages and tablets and capsules being more convenient to the lifestyle of adolescents.

Paediatric practice requires a range of dosage forms that are acceptable at different ages and abilities and a range of strengths or concentrations allowing administration of the correct age-related dose. Seriously ill children will require intravenous drug administration and will prefer this to frequent intramuscular injections. For less serious illness and long-term administration the oral route will be preferred but other routes such as buccal, nasal, transdermal and rectal can be useful in some circumstances.

The age at which children take tablets or capsules is a factor of importance to their safety so that inadvertent inhalation and choking are avoided but is also of great importance to manufacturers. Tablet formulations are generally easier and cheaper to develop, manufacture, transport, store and dispense than liquid medicines. There is little information in the literature but it is generally believed that traditional tablets may be accepted by children of school age, although this will depend on the size and shape of the tablet and patient factors such as the taste of liquid medicine alternatives. In fact, advances in pharmaceutical technology have resulted in the development of many different types of tablets such as melts, chewable and oro-dispersible tablets, and it is technically possible that appropriate tablet formulations could be made available for children of most ages, but at a cost.

Challenges with oral liquid formulations

The dose and volume of liquid medicines may be limited by the solubility of drug substances requiring the addition of cosolvent and surfactant excipients. Physical, chemical and microbiological stability must be assured with buffering agents, antioxidants and preservatives. Of crucial importance is the ability to mask unpleasant taste with sweeteners and flavours. If this is not achievable, more sophisticated formulation approaches such as encapsulation of drug particles, may be required. These more complex formulation approaches bring higher technical challenges and consequently, research and development will be more lengthy and costly.

Formulation homogeneity is required and dosing devices such as droppers or syringes may be required for accurate dosing.

There are limitations on choice and concentration of excipients for paediatric patients.

Solid dosage forms

A wide variety of solid dosage forms is now available including powders (e.g. Viracept® oral powder (nelfinavir mesylate, Pfizer), granules (e.g. Singulair® oral granule (Montelukast Na, Merck) and sprinkles (e.g. Depakote® Sprinkle capsules (Divalproex Na, Abbott). These are usually mixed with specified food or drink and are easy to swallow. Taste is again important; there is risk of incomplete ingestion and consequently a reduction in the dose given. Potential for technical challenges include powder processing, packaging, stability and dose extraction.

A variety of modern tablet preparations is available such as fast dispersing dosage forms (FDDFs), for example Calpol Fast Melts® (Pfizer Consumer Health), Nurofen® Meltlets (Crookes Healthcare), Benadryl® orodispersible tablets. None of the products currently has a licence for children less than 6 years of age, primarily due to the dose strengths available. These products are placed in the mouth where they 'melt' on the tongue in a small amount of saliva or can be dispersed in a small amount of liquid on a spoon. They are easy to administer providing that taste is acceptable and they provide accuracy of dose. However, many of these technologies are proprietary and consequently will require licensing agreements Development costs are higher than for conventional oral dosage forms. Examples include Zydis™ (Scherer), OralSolv™ (Cima), WOWtab™ (Yamanouchi), Films (LTS Lohman)

Tan and Cranswick NE (2003) have shown that in Australia 70–80% of products suitable for children have inadequate dosing information in the SPC and that in 25% of products licensed for children, dosage forms are

unsuitable for the intended ages. However, if there is the commercial incentive of a large market for a common illness such as pain or vomiting or for OTC products, a complete and varied portfolio of products can be made available as shown by paracetamol and ondansetron.

An ideal formulation for children will allow minimal dosage and frequency; will have one dosage form to fit all or a full range; will have minimal impact on lifestyle; a minimum of nontoxic excipients and will have convenient, easy, reliable administration. It should also be easily produced, elegant, stable, cheap and commercially viable. The challenge in achieving this should not be underestimated.

Challenges and knowledge gaps

There are many gaps in our knowledge about paediatric formulations and many challenges for industry to face if suitable preparations are to be available for all age ranges. These include

- acceptable dose volumes and sizes
- safety, e.g. risk of aspiration or choking for solid dosage forms
- excipient acceptability
- taste (and how best to assess during development).

Information is available with a CHMP points to consider formulation document in draft. Undoubtedly more research and clinical feedback will be valuable since if a formulation has poor patient acceptability, it affects compliance, prescribing practices and ultimately commercial viability.

Conclusions

Determining the correct dose and our ability to deliver it to the child successfully are equally important. We need a variety of different dosage forms to satisfy clinical need, varying dose requirement with age; ability and preference. The availability of appropriate dosage forms is limited even when the medicine is authorized for children. EU regulations and incentives may improve the situation from 2007 and a points to consider document on 'formulations of choice for the paediatric population' should better inform the industry. We need to encourage and work with manufacturers to adapt medicines to the needs of children but should also ensure that pharmacists and carers have information to adapt dosage forms safely and to extemporaneously formulate if necessary. Clearly more research and development is required.

Reference

1 Tan E, Cranswick NE, Rayner CR, Chapman CB. Dosing information for paediatric patients: are they really 'therapeutic orphans'? Med J Aust 2003; 179 (4): 195–8.